For the use of a Registered Medical Practitioner only

PRESCRIBING INFORMATION

℞ Sorafenib Tablets IP 200 mg
SORAFGEN-200

1. Generic Name
Sorafenib Tablets IP 200 mg

2. Qualitative and Quantitative Composition
Each film coated tablet contains:

Sorafenib Tosylate IP	
Eq. to Sorafenib	200 mg
Excipients	q.s
Colours: Ferric Oxide USP-NF Red & Titanium Dioxide IP	

3. Dosage Form & Strength
Sorafenib Tablets IP 200 mg for oral use

4. Clinical Particulars
4.1 Therapeutic Indications
Sorafenib is indicated for the treatment of:
- patients with advanced renal cell carcinoma
- hepatocellular carcinoma
- patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine

4.2 Posology and Method of administration
The recommended dose of sorafenib in adults is 400 mg sorafenib (two tablets of 200 mg) twice daily without food (at least 1 hour before or 2 hours after a meal)
Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.
Posology adjustments
Temporary interruption of sorafenib is recommended in patients undergoing major surgical procedures.
Management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy (Table 1).

Table 1: Adverse Reactions Requiring Dose Modification of Sorafenib

Adverse Reaction	CTCAE Grade	Action	Dose Reduce and Resume Sorafenib
Cardiovascular Events			
Cardiac Ischemia and/or Infarction	Grade 2 and above	Permanently discontinue	Do not resume
Congestive Heart Failure	Grade 3	Interrupt[a] until ≤ Grade 1	Decrease one dose level[b,c]
	Grade 4	Permanently discontinue	Do not resume
Hemorrhage requiring medical intervention	Grade 2 and above	Permanently discontinue	Do not resume
Hypertension	Grade 2 asymptomatic and diastolic pressure 90-99 mm Hg	Treat with anti-hypertensive therapy	Continue sorafenib dosing as scheduled and closely monitor blood pressure
	Grade 2 (symptomatic/ persistent) OR Grade 2 symptomatic increase by >20 mm Hg (diastolic) or >140/90 mm Hg if previously within normal limits OR Grade 3	Interrupt until symptoms resolve and diastolic blood pressure < 90 mm Hg	Treat with antihypertensives. Reduce dose to one dose levelc when resumed. If needed, reduce another dose level.[b,c]
	Grade 4	Permanently discontinue	Do not resume
Gastrointestinal perforation	Any grade	Permanently discontinue	Do not resume
QT prolongation	Monitor electrolytes and electrocardiograms If QTc is >500 milliseconds or for an increase from baseline of 60 milliseconds or greater	Interrupt Correct electrolyte abnormalities (magnesium, potassium, calcium).	Use medical judgement before restarting
Severe drug induced liver injury (DILI)	> Grade 3 ALT in the absence of another caused AST/ALT > 3xULN with bilirubin > 2xULN in the absence of another caused	Permanently discontinue	Do not resume
Non-hematological Toxicities	Grade 2	Treat on time	Decrease one dose level[c]
	Grade 3		
	1st occurrence	Interrupt until ≤ Grade 2	Decrease one dose level[c]
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt until ≤ Grade 2	Decrease two dose level[c]
	4th occurrence	Interrupt until ≤ Grade 2	Decrease three dose level[c]
	Grade 4	Permanently discontinue	Do not resume

[a] If no recovery after 30 day interruption, treatment will be discontinued unless the patient is deriving clinical benefit
[b] If more than 2 dose reductions are required, treatment will be discontinued
[c] Hepatocellular and renal cell carcinoma (400 mg daily, 200 mg daily or 400 every other day) and thyroid cancer (800 mg to 600 mg, 400 mg, and 200 mg). See details below for reduction per indication
[d] In addition, any grade Alkaline phosphatase increase in the absence of known bone pathology and Grade 2 or worse Bilirubin increase; Any 1 of the following: INR ≥ 1.5, Ascites and/or encephalopathy in the absence of underlying cirrhosis or other organ failure considered to be due to DILI.

When dose reduction is necessary during the treatment of hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), the sorafenib dose should be reduced to 400 mg sorafenib once daily. If additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose (two tablets of 200 mg) every other day.
Suggested dose modifications for dermatologic toxicities are outlined in Table 2.
Table 2: Suggested Dose Modifications for Dermatologic Toxicities in Patients with Hepatocellular Carcinoma, Renal Cell Carcinoma and Differentiated Thyroid Carcinoma

Dermatologic Toxicity Grade	Occurrence	Sorafenib Dose Modification	
		Hepatocellular and Renal Cell Carcinoma	Differentiated Thyroid Carcinoma
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below	Decrease sorafenib dose to 600 mg daily If no improvement within 7 days, see below
	No improvement within 7 days at reduced dose or 2nd and 3rd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1	Interrupt sorafenib until resolved or improved to Grade 1
		When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day)	If sorafenib is resumed, decrease dose (see Table 3)
	4th occurrence	Discontinue Sorafenib treatment	
Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living	1st occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1	Interrupt sorafenib until resolved or improved to Grade 1
		When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day)	Sorafenib is resumed, decrease dose by one dose level (see Table 3)
	2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1	Interrupt sorafenib until resolved or improved to Grade 1
		When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day)	When sorafenib is resumed, decrease dose by 2 dose levels (see Table 3)
	3rd occurrence	Discontinue sorafenib treatment	

Dose modifications for Differentiated Thyroid Carcinoma
Table 3: Recommended Doses for Patients with Differentiated Thyroid Carcinoma Requiring Dose Reduction

Dose Reduction	Sorafenib Dose	
First dose reduction	600 mg daily dose	400 mg and 200 mg 12 hours apart (2 tablets and 1 tablet 12 hours apart – either dose can come first)
Second dose reduction	400 mg daily dose	200 mg twice daily (1 tablet twice daily)
Third dose reduction	200 mg daily dose	200 mg once daily (1 tablet twice daily)

When dose reduction is necessary for dermatologic toxicities, reduce the sorafenib dose as indicated in Table 2.
Following improvement of Grade 2 or 3 dermatologic toxicity to Grade 0–1 after at least 28 days of treatment on a reduced dose of sorafenib, the dose of sorafenib may be increased one dose level from the reduced dose. Approximately 50% of patients requiring a dose reduction for dermatologic toxicity are expected to meet these criteria for resumption of the higher dose and roughly 50% of patients resuming the previous dose are expected to tolerate the higher dose (that is, maintain the higher dose level without recurrent Grade 2 or higher dermatologic toxicity).
Paediatric population
The safety and efficacy of sorafenib in children and adolescents aged <18 years have not yet been established. No data are available.
Elderly population
No dose adjustment is required in the elderly (patients above 65 years of age).
Renal impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis.
Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.
Hepatic impairment
No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. No data is available on patients with Child Pugh C (severe) hepatic impairment.
Method of administration
For oral use.
It is recommended that sorafenib should be administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer

4.4 Special warnings and precautions for use
Dermatological toxicities
Hand foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with sorafenib. Rash and hand foot skin reaction are usually CTC (Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib. Management of dermatological toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib.
There have been reports of severe dermatologic toxicities, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These cases may be life-threatening. Discontinue sorafenib if SJS or TEN are suspected.
Hypertension
An increased incidence of arterial hypertension was observed in sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of sorafenib should be considered.Regularly (monitor blood pressure weekly during the first 6 weeks of sorafenib).
Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating sorafenib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.
Hypoglycaemia
Decreases in blood glucose, in some cases clinically symptomatic and requiring hospitalization due to loss of consciousness, have been reported during sorafenib treatment. In case of symptomatic hypoglycaemia, sorafenib should be temporarily interrupted. Blood glucose levels in diabetic patients should be checked regularly in order to assess if anti-diabetic medicinal product's dosage needs to be adjusted.
Haemorrhage
An increased risk of bleeding may occur following sorafenib administration. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of sorafenib should be considered.
Cardiac ischaemia and/or infarction
In a randomised, placebo-controlled, double-blind study, the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the sorafenib group (4.9 %) compared with the placebo group (0.4 %). In study 3, the incidence of treatment-emergent cardiac ischaemia/infarction events was 2.7 % in sorafenib patients compared with 1.3 % in the placebo group. Patients with unstable coronary artery disease or recent myocardial infarction were excluded from these studies. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischaemia and/or infarction.
QT interval prolongation
Sorafenib has been shown to prolong the QT/QTc interval, which may lead to an increased risk for ventricular arrhythmias. Use sorafenib with caution in patients who have, or may develop prolongation of QTc, such as patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using sorafenib in these patients, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium, calcium) should be considered.Interrupt Sorafenib if QTc interval is greater than 500 milliseconds or for an increase from baseline of 60 milliseconds or greater.
Gastrointestinal perforation
Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking sorafenib. In some cases, this was not associated with apparent intra-abdominal tumour. Sorafenib therapy should be discontinued.
Hepatic impairment
No data is available on patients with Child Pugh C (severe) hepatic impairment. Since sorafenib is mainly eliminated via the hepatic route exposure might be increased in patients with severe hepatic impairment.
Warfarin co-administration
Infrequent bleeding events or elevations in the International Normalised Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking concomitant warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.
Wound healing complications
No formal studies of the effect of sorafenib on wound healing have been conducted.
Temporary interruption of sorafenib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sorafenib therapy following a major surgical intervention should be based on clinical judgement of adequate wound healing.
Elderly population
Cases of renal failure have been reported. Monitoring of renal function should be considered.
Drug-drug interactions
Caution is recommended when administering sorafenib with compounds that are metabolised/eliminated predominantly by the UGT1A1 (e.g. irinotecan) or UGT1A9 pathways.
Caution is recommended when sorafenib is co-administered with docetaxel.
Co-administration of neomycin or other antibiotics that cause major ecological disturbances of the gastrointestinal microflora may lead to a decrease in sorafenib bioavailability. The risk of reduced plasma concentrations of sorafenib should be considered before starting a treatment course with antibiotics.
Higher mortality has been reported in patients with squamous cell carcinoma of the lung treated with sorafenib in combination with platinum-based chemotherapies. In two randomised trials investigating patients with Non-Small Cell Lung Cancer in the subgroup of patients with squamous cell carcinoma treated with sorafenib as add-on to paclitaxel/carboplatin, the HR for overall survival was found to be 1.81 (95% CI 1.19; 2.74) and as add-on to gemcitabine/cisplatin 1.22 (95% CI 0.82; 1.80). No single cause of death dominated, but higher incidence of respiratory failure, haemorrhages and infectious adverse events were observed in patients treated with sorafenib as add-on to platinum-based chemotherapies.
Disease specific warnings
Differentiated thyroid cancer (DTC)
Before initiating treatment, physicians are recommended to carefully evaluate the prognosis in the individual patient considering maximum lesion size, symptoms related to the disease and progression rate.
Management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy. In study 5, 37% of subjects had dose interruption and 35% had dose reduction already in cycle 1 of sorafenib treatment.
Dose reductions were only partially successful in alleviating adverse reactions. Therefore, repeat evaluations of benefit and risk is recommended taking anti-tumour activity and tolerability into account.
Haemorrhage in DTC
Due to the potential risk of bleeding, tracheal, bronchial, and oesophageal infiltration should be treated with localized therapy prior to administering sorafenib in patients with DTC.
Hypocalcaemia in DTC
When using sorafenib in patients with DTC, close monitoring of blood calcium level is recommended. In clinical trials, hypocalcaemia was more frequent and more severe in patients with DTC, especially with a history of hypoparathyroidism, compared to patients with renal cell or hepatocellular carcinoma. Hypocalcaemia grade 3 and 4 occurred in 6.8% and 3.4% of sorafenib-treated patients with DTC. Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes.
TSH suppression in DTC
In a clinical study, increases in TSH levels above 0.5mU/L were observed in sorafenib treated patients. When using sorafenib in DTC patients, close monitoring of TSH level is recommended.
Renal cell carcinoma
High Risk Patients, according to MSKCC (Memorial Sloan Kettering Cancer Center) prognostic group, were not included in the phase III clinical study in renal cell carcinoma, and benefit-risk in these patients has not been evaluated.

4.5 Interaction with other medicinal products and other forms of interaction
Inducers of metabolic enzymes
Administration of rifampicin for 5 days before administration of a single dose of sorafenib resulted in an average 37 % reduction of sorafenib AUC. Other inducers of CYP3A4 activity and/or glucuronidation (e.g. Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations.
CYP3A4 inhibitors
Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of sorafenib. These data suggest that clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.
CYP2B6, CYP2C8 and CYP2C9 substrates
Sorafenib inhibited CYP2B6, CYP2C8 and CYP2C9 in vitro with similar potency. However, in clinical pharmacokinetic studies, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, or paclitaxel, a CYP2C8 substrate, did not result in a clinically meaningful inhibition. These data suggest that sorafenib at the recommended dose of 400 mg twice daily may not be an in vivo inhibitor of CYP2B6 or CYP2C8.
Additionally, concomitant treatment with sorafenib and warfarin, a CYP2C9 substrate, did not result in changes in mean PT-INR compared to placebo. Thus, also the risk for a clinically relevant in vivo inhibition of CYP2C9 by sorafenib may be expected to be low. However, patients taking warfarin or phenprocoumon should have their INR checked regularly.
CYP3A4, CYP2D6 and CYP2C19 substrates
Concomitant administration of sorafenib and midazolam, dextromethorphan or omeprazole, which are substrates for cytochromes CYP3A4, CYP2D6 and CYP2C19 respectively, did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes are unlikely.
UGT1A1 and UGT1A9 substrates
In vitro, sorafenib inhibited glucuronidation via UGT1A1 and UGT1A9. The clinical relevance of this finding is unknown.
In vitro studies of CYP enzyme induction
CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4.
P-gp-substrates
In vitro, sorafenib has been shown to inhibit the transport protein p-glycoprotein (P-gp). Increased plasma concentrations of P-gp substrates such as digoxin cannot be excluded with concomitant treatment with sorafenib.
Combination with other anti-neoplastic agents
In clinical studies sorafenib has been administered with a variety of other anti-neoplastic agents at their commonly used dosing regimens including gemcitabine, cisplatin, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, irinotecan, docetaxel and cyclophosphamide. Sorafenib had no clinically relevant effect on the pharmacokinetics of gemcitabine, cisplatin, carboplatin, oxaliplatin or cyclophosphamide.
Paclitaxel/carboplatin
Administration of paclitaxel (225 mg/m^2) and carboplatin (AUC = 6) with sorafenib (≤ 400 mg twice daily), administered with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration), resulted in no significant effect on the pharmacokinetics of paclitaxel.
Co-administration of paclitaxel (225 mg/m^2, once every 3 weeks) and carboplatin (AUC=6) with sorafenib (400 mg twice daily, without a break in sorafenib dosing) resulted in a 47% increase in sorafenib exposure, a 29% increase in paclitaxel exposure and a 50% increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin were unaffected.
These data indicate no need for dose adjustments when paclitaxel and carboplatin are co-administered with sorafenib with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration). The clinical significance of the increases in sorafenib and paclitaxel exposure, upon co-administration of sorafenib without a break in dosing, is unknown.
Capecitabine
Co-administration of capecitabine (750-1050 mg/m^2 twice daily, Days 1-14 every 21 days) and sorafenib (200 or 400 mg twice daily, continuous uninterrupted administration) resulted in no significant change in sorafenib exposure, but a 15-50% increase in capecitabine exposure and a 0-52% increase in 5-FU exposure. The clinical significance of these small to modest increases in capecitabine and 5-FU exposure when co-administered with sorafenib is unknown.
Doxorubicin/Irinotecan
Concomitant treatment with sorafenib resulted in a 21 % increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolised by the UGT1A1 pathway, there was a 67 - 120 % increase in the AUC of SN-38 and a 26 - 42 % increase in the AUC of irinotecan. The clinical significance of these findings is unknown.

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Reason for change: Change in brand design and artwork revised

Docetaxel
Docetaxel (75 or 100 mg/m^2 administered once every 21 days) when co-administered with sorafenib (200 mg twice daily or 400 mg twice daily administered on Days 2 through 19 of a 21-day cycle with a 3-day break in dosing around administration of docetaxel) resulted in a 36-80 % increase in docetaxel AUC and a 16-32 % increase in docetaxel C_{max}. Caution is recommended when sorafenib is co-administered with docetaxel.
Combination with other agents
Neomycin
Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib, resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average exposure to sorafenib decreased by 54%. Effects of other antibiotics have not been studied, but will likely depend on their ability to interfere with microorganisms with glucuronidase activity.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
There are no data on the use of sorafenib in pregnant women. Studies in animals have shown reproductive toxicity including malformations. In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to cause harmful effects on the foetus. Sorafenib should not be used during pregnancy unless clearly necessary, after careful consideration of the needs of the mother and the risk to the foetus.
Women of childbearing potential must use effective contraception during treatment.
Lactation
It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because sorafenib could harm infant growth and development, women must not breast-feed during sorafenib treatment.
Fertility
Results from animal studies further indicate that sorafenib can impair male and female fertility

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. There is no evidence that sorafenib affects the ability to drive or to operate machinery.

4.8 Undesirable Effects
The most important serious adverse reactions were myocardial infarction/ischaemia, gastrointestinal perforation, drug induced hepatitis, haemorrhage, and hypertension/ hypertensive crisis.
The most common adverse reactions were diarrhoea, fatigue, alopecia, infection, hand foot skin reaction (corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA) and rash.
Infections and infestations
Very common: infection
Common: folliculitis
Blood and lymphatic system disorders
Very common: lymphopenia, leucopenia
Common: Neutropenia, anaemia, thrombocytopenia
Immune system disorders
Uncommon: hypersensitivity reactions (including skin reactions and urticaria) anaphylactic reaction
Rare: angioedema
Endocrine disorders
Common: hypothyroidism
Uncommon: hyperthyroidism
Metabolism and nutrition disorder
Very common: anorexia, hypo-phosphataemia
Common: hypocalcaemia, hypokalaemia, hyponatraemia, hypoglycaemia
Uncommon: dehydration
Psychiatric disorders
Common: depression
Nervous system disorders
Common: peripheral sensory neuropathy, dysgeusia
Uncommon: reversible posterior leukoencephalopathy
Not known: encephalopathy
Ear and labyrinth disorders
Common: tinnitus
Cardiac disorders
Common: congestive heart failure, myocardial ischaemia and infarction
Rare: QT prolongation
Vascular disorders
Very Common: haemorrhage (inc. gastrointestinal, respiratory tract and cerebral haemorrhage), hypertension
Common: flushing
Uncommon: hypertensive crisis
Not known: aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders
Common: rhinorrhoea, dysphonia
Uncommon: interstitial lung disease-like events (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.
Gastrointestinal disorders
Very Common: diarrhoea, nausea, vomiting, constipation
Common: stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia, gastro oesophageal reflux disease
Uncommon: pancreatitis, gastritis, gastrointestinal perforations
Hepatobiliary disorders
Uncommon: increase in bilirubin and jaundice, cholecystitis, cholangitis
Rare: drug induced hepatitis
Skin and subcutaneous tissue disorders
Very Common: dry skin, rash, alopecia, hand foot skin reaction, erythema, pruritus
Common: keratoacanthoma/ squamous cell cancer of the skin, dermatitis exfoliative, acne, skin desquamation, hyperkeratosis
Uncommon: eczema, erythema multiforme
Rare: radiation recall dermatitis, Stevens-Johnson syndrome, leucocytoclastic vasculitis, toxic epidermal necrolysis
Musculo-skeletal and connective tissue disorders
Very Common: arthralgia
Common: myalgia, muscle spasms
Rare: rhabdomyolysis
Renal and urinary disorders
Common: renal failure, proteinuria
Rare: nephrotic syndrome
Reproductive system and breast disorders
Common: erectile dysfunction
Uncommon: gynaecomastia
General disorders and administration site conditions
Very Common: fatigue, pain (including mouth, abdominal, bone, tumour pain and headache), fever
Common: asthenia, influenza like illness, mucosal inflammation
Investigations
Very Common: weight decreased, increased amylase, increased lipase
Common: transient increase in transaminases
Uncommon: transient increase in blood alkaline phosphatase, INR abnormal, prothrombin level abnormal.
Reporting of suspected adverse reactions
Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form (**form.heteroworld.com**) or by **Hetero Helpline No.1800-120-8689.**

4.9 Overdose
There is no specific treatment for sorafenib overdose. The highest dose of sorafenib studied clinically is 800 mg twice daily. The adverse events observed at this dose were primarily diarrhoea and dermatological events. In the event of suspected overdose sorafenib should be withheld and supportive care instituted where necessary.

5. Pharmacological Properties
5.1 Mechanism of action
Sorafenib is a multikinase inhibitor that decreases tumour cell proliferation in vitro. Sorafenib inhibits tumour growth of a broad spectrum of human tumour xenografts in athymic mice accompanied by a reduction of tumour angiogenesis. Sorafenib inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, c-KIT, and FLT-3) and in the tumour vasculature (CRAF, VEGFR-2, VEGFR-3, and PDGFR-ß). RAF kinases are serine/threonine kinases, whereas c-KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-ß are receptor tyrosine kinases.

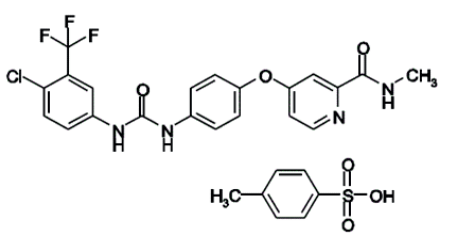
5.2 Pharmacodynamic properties
The safety and efficacy of sorafenib in the treatment of advanced renal cell carcinoma (RCC) were investigated in two clinical studies:
Study 1 (study 11213) was a Phase III, multi-centre, randomised, double blind, placebo-controlled study in 903 patients. Only patients with clear cell renal carcinoma and low and intermediate risk MSKCC (Memorial Sloan Kettering Cancer Center) were included. The primary endpoints were overall survival and progression-free survival (PFS).
Approximately half of the patients had an ECOG performance status of 0, and half of the patients were in the low risk MSKCC prognostic group.
PFS was evaluated by blinded independent radiological review using RECIST criteria. The PFS analysis was conducted at 342 events in 769 patients. The median PFS was 167 days for patients randomised to sorafenib compared to 84 days for placebo patients (HR = 0.44; 95 % CI: 0.35 - 0.55; p < 0.000001). Age, MSKCC prognostic group, ECOG PS and prior therapy did not affect the treatment effect size.
An interim analysis (second interim analysis) for overall survival was conducted at 367 deaths in 903 patients. The nominal alpha value for this analysis was 0.0094. The median survival was 19.3 months for patients randomised to sorafenib compared to 15.9 months for placebo patients (HR = 0.77; 95 % CI: 0.63 - 0.95; p = 0.015). At the time of this analysis, about 200 patients had crossed-over to sorafenib from the placebo group.
Study 2 was a Phase II, discontinuation study in patients with metastatic malignancies, including RCC. Patients with stable disease on therapy with sorafenib were randomised to placebo or continued sorafenib therapy. Progression-free survival in patients with RCC was significantly longer in the sorafenib group (163 days) than in the placebo group (41 days) (p = 0.0001, HR = 0.29).

5.3 Pharmacokinetic properties
Absorption
After administration of sorafenib tablets the mean relative bioavailability is 38 - 49 % when compared to an oral solution. The absolute bioavailability is not known. Following oral administration sorafenib reaches peak plasma concentrations in approximately 3 hours. When given with a high-fat meal sorafenib absorption was reduced by 30 % compared to administration in the fasted state.
Distribution
Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered twice daily. *In vitro* binding of sorafenib to human plasma proteins is 99.5 %.
Multiple dosing of sorafenib for 7 days resulted in a 2.5- to 7-fold accumulation compared to single dose administration. Steady state plasma sorafenib concentrations are achieved within 7 days, with a peak to trough ratio of mean concentrations of less than 2.
The steady-state concentrations of sorafenib administered at 400 mg twice daily were evaluated in DTC, RCC and HCC patients. The highest mean concentration was observed in DTC patients (approximately twice that observed in patients with RCC and HCC), though variability was high for all tumour types. The reason for the increased concentration in DTC patients is unknown.
Metabolism
Sorafenib is metabolised primarily in the liver and undergoes oxidative metabolism, mediated by CYP 3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib conjugates may be cleaved in the gastrointestinal tract by bacterial glucuronidase activity, allowing reabsorption of unconjugated active substance. Co-administration of neomycin has been shown to interfere with this process, decreasing the mean bioavailability of sorafenib by 54%.
Sorafenib accounts for approximately 70 - 85 % of the circulating analytes in plasma at steady state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide, shows in vitro potency similar to that of sorafenib. This metabolite comprises approximately 9 - 16 % of circulating analytes at steady state.
Excretion
The elimination half-life of sorafenib is approximately 25 - 48 hours.

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96 % of the dose was recovered within 14 days, with 77 % of the dose excreted in faeces, and 19 % of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51 % of the dose, was found in faeces but not in urine, indicating that biliary excretion of unchanged active substance might contribute to the elimination of sorafenib.

6. Nonclinical Properties
6.1 Animal Toxicology or Pharmacology
The preclinical safety profile of sorafenib was assessed in mice, rats, dogs and rabbits.
Repeat-dose toxicity studies revealed changes (degenerations and regenerations) in various organs at exposures below the anticipated clinical exposure (based on AUC comparisons).
After repeated dosing to young and growing dog's effects on bone and teeth were observed at exposures below the clinical exposure. Changes consisted in irregular thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate and alterations of the dentin composition. Similar effects were not induced in adult dogs.
The standard program of genotoxicity studies was conducted and positive results were obtained as an increase in structural chromosomal aberrations in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity in the presence of metabolic activation was seen. Sorafenib was not genotoxic in the Ames test or in the in vivo mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final active substance (< 0.15 %), was positive for mutagenesis in an in vitro bacterial cell assay (Ames test). Furthermore, the sorafenib batch tested in the standard genotoxicity battery included 0.34 % PAPE.
Carcinogenicity studies have not been conducted with sorafenib.
No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. An adverse effect on male and female fertility can however be expected because repeat-dose studies in animals have shown changes in male and female reproductive organs at exposures below the anticipated clinical exposure (based on AUC). Typical changes consisted of signs of degeneration and retardation in testes, epididymides, prostate, and seminal vesicles of rats. Female rats showed central necrosis of the corpora lutea and arrested follicular development in the ovaries. Dogs showed tubular degeneration in the testes and oligospermia.
Sorafenib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below the clinical exposure. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased number of external and visceral malformations.
Environmental Risk assessment studies have shown that sorafenib tosylate has the potential to be persistent, bioaccumulative and toxic to the environment.

7. Description
Sorafenib a kinase inhibitor, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4{3[4Chloro3(trifluoromethyl)phenyl]ureido}phenoxy)N2methylpyridine-2-carboxamide 4-methylbenzenesulfonate and its structural formula is:



8. Pharmaceutical Particulars
8.1 Incompatibilities
Not applicable

8.2 Shelf-life
24 months

8.3 Packing Information
120 CC HDPE Container Pack : Contains 120 Tablets

8.4 Storage and handling instructions
Store at a temperature not exceeding 30°C. Protect from light.
Keep out of reach of children.
Keep container tightly closed.
Dispense in original container.
Do not use if seal over bottle opening is broken or missing.

9. Patient Counselling Information
Do not take sorafenib if you:
- are allergic to sorafenib or any of the other ingredients in sorafenib. See the end of this leaflet for a complete list of ingredients in sorafenib.
- have squamous cell lung cancer and receive carboplatin and paclitaxel.

Before taking sorafenib, tell your healthcare provider about all of your medical conditions including if:
- you have heart problems including a condition called “congenital long QT syndrome”
- you have chest pain
- you have abnormal magnesium, potassium, or calcium blood levels
- you have bleeding problems
- you have high blood pressure
- you plan to have any surgical procedures or have had recent surgery
- you are pregnant or plan to become pregnant. sorafenib may harm your unborn baby.

Tell your healthcare provider right away if you become pregnant during treatment with sorafenib.
For females who are able to become pregnant:
✓ Your healthcare should do a pregnancy test before you start treatment with sorafenib.
✓ For females who are able to become pregnant: Use effective birth control (contraception) during your treatment with sorafenib and for 6 months after the last dose of sorafenib.
✓ For males with female partners who are able to become pregnant: Use effective birth control (contraception) during your treatment with sorafenib and for 3 months after the last dose of sorafenib.
- you are breastfeeding or plan to breastfeed. It is not known if sorafenib passes into your breast milk. Do not breastfeed during treatment with sorafenib and for 2 weeks after receiving the last dose of sorafenib.

Tell your healthcare provider about all the medicines you take, including prescription and over-the−counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take the medicine warfarin.

10. Details of Manufacturer
Hetero Labs Limited (Unit-I)
Village: Kalyanpur, Chakkan Road,
Tehsil: Baddi, Distt.: Solan,
Himachal Pradesh-173 205, India.

11. Details of permission or licence number with date
MNB/06/328, dated: 21-01-2021

12. Date of revision
09-09-2024

GENYGI
Marketed by:
Genygi Life Sciences Private Limited
SS - 29, Second Floor, Aditya Mega Mall,
Plot # 9D, Delhi - 110032

2073713-01

Dimension: 290x315 mm,
Colour: Black
Spec: 54 gsm, Maplitho Paper
Folding size: 72.5x39.37 mm
Reason for change: Change in brand design and artwork revised